Development of a stem-cell based approach to interpret global effects of genetic variants contributing to neurodevelopmental disease risk

Grant Award Details

Development of a stem-cell based approach to interpret global effects of genetic variants contributing to neurodevelopmental disease risk

Grant Type: Foundation - Discovery Stage Research Projects

Grant Number: DISC0-13808

Project Objective: To establish a high throughput single cell base editing approach (scBE-seq) in hiPSC, and apply it to the interrogation of pathogenicity of a large number of SNVs introduced into 2 genes known to play a role in neurodevelopmental diseases.

Investigator:

Name:	Alexis Komor
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Neurological Disorders, Rett's Syndrome

Human Stem Cell Use: iPS Cell

Award Value: $1,518,982

Status: Pre-Active

Grant Application Details

Application Title: Development of a stem-cell based approach to interpret global effects of genetic variants contributing to neurodevelopmental disease risk

Public Abstract:

Research Objective

We are developing a strategy to characterize the disease-relevance of hundreds of mutations across diverse genetic backgrounds using stem cells

Impact

Understanding how mutations impact cellular function can identify treatments for genetic diseases, but currently less than 1% of identified mutations have a known function.

Major Proposed Activities

- Identify optimal conditions for SNV library introduction in hiPCSs and characterize the global impact of individual mutations in ERCC2 and MECP2 on transcription, chromatin state, and mutational rates
- Develop a computational pipeline to design SNV libraries and analyze data from our method, scBE-seq
- Employ scBE-seq to study the impact of libraries of mutations in ERCC2 and MECP2 during the in vitro neurodifferentiation of hiPSCs into cortical organoids
- Analyze scBE-seq data and compare with orthogonal datasets for clinical interpretation of genetic variation

Statement of Benefit to California:

An overrepresentation of European human genome sequencing data has generated inequities in regenerative and precision medicine efforts. We propose here to develop a more equitable strategy to characterize the disease-relevance of mutations from diverse populations. Our project will identify new preventative strategies, treatments, and cures for genetic diseases applicable to a variety of ethnic groups, and will therefore benefit the State of California and its highly ethnically diverse citizens.

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